REMARKS

Claims 1-11, 14-17, 19 and 32 are currently pending. Claims 12-13 and 18 have are canceled by this amendment. Claims 14 and 32 have been amended. The amendment to Claim 14 is to correct a typographical error and the amendment to Claim 32 is supported by Examples 3, 9, and 10, thus no new matter has been entered by this amendment. For the reasons detailed below, Applicants respectfully request the rejections be withdrawn and the claims be allowed to issue.

The Claims are Definite

Claim 32 stands newly rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for filing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner contends that the claim is directed to a method for isolating a population of differentiated neural cells wherein those cells are transfected with one or more nucleic acids encoding an ATF5 inhibitor and a fluorescent protein and isolation of the differentiated neural cells is mediated by detection of expression of fluorescent protein. The Examiner asserts that it is not clear how expression of fluorescent protein is related to differentiated neural cells.

Without acquiescing in the propriety of the Examiner's rejection, and solely in the interest of expediting prosecution of the instant application, Applicants have amended Claim 32 such that the claimed method relates to the transfection of a nucleic acid comprising a sequence encoding an ATF5 inhibitor and a sequence encoding a fluorescent protein. As illustrated in Examples 9 and 10 of the instant specification, measurement of fluorescence allows for the

selection of differentiation of nerve cells after transfection with the claimed nucleic acid. In light of the foregoing, Applicants respectfully request withdrawal of the instant rejection.

The Claims have Sufficient Written Description Support

Claim 32 stands rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the Written Description requirement. In particular the Examiner contends that the method described in Claim 32 recites the use of a "fluorescent protein", which encompasses a genus of fluorescent proteins. The Examiner asserts that such a genus includes "new matter" as the specification allegedly only provides support for the use of the species eGFP in such a method. Applicants respectfully traverse this rejection.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. (See Eli Lilly, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed Cir 1997). A "representative number of species" means that the species which are adequately described are representative of the entire genus. Accordingly, in situations where the genus can be adequately described by a single species, that single species is considered a representative number of species. (See USPTO Written Description Guidelines, Fed. Reg., Vol. 66, No. 4, pages 1099-1111, 1106 (2001)). Furthermore, it is well established that "use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art

to that class of compounds. Occasionally, a functional recitation of those known compounds in the specification may be sufficient as that description." (See In re Herschler, 591 F.2d 693, 697, 200 USPQ 711, 714 (CCPA 1979) (disclosure of corticosteroid in DMSO sufficient to support claims drawn to a method of using a mixture of a "physiologically active steroid" and DMSO).

Applicants note that the instant application describes the auxiliary use of eGFP as a marker throughout the specification, and in particular in Examples, 8-10 (paragraphs [0163] - [0165]). Applicants submit that the functional characteristic of eGFP, specifically, the ability to be used as a marker both at the protein and nucleic acid levels (as described in paragraph [0090]), is equally applicable to the claimed genus of fluorescent proteins. Furthermore, the Examiner has not presented any evidence that the functional recitation of eGFP would be insufficient to lead one of skill in the art to the genus of fluorescent protein markers generally. Accordingly, Applicants respectfully request withdrawal of the instant rejection.

The Claims are Enabled

The Examiner has maintained her rejection of Claims 6, 8-11, 15, 17 and 19 under 35 U.S.C. § 112, first paragraph, as being unenabled. The Examiner contends that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or which it is most nearly connected, to make and/or use the invention. In particular, the Examiner contends that one of skill in the art would have to engage in excessive trial and error experimentation to determine: (1) the appropriate dosages of ATF5 inhibitors, and/or (2) the appropriate in vivo administration techniques to practice the claimed invention. Applicants respectfully traverse this rejection.

As a preliminary matter applicants note that the Examiner has cited In re Gardner, Roe and Willey, 427 F.2d 786 (CCPA 1970) as establishing that a failure to disclosure of effective drug dosages renders claims to methods of treatment using that drug insufficiently enabled. Regardless of the propriety of that position, Applicants respectfully point out that the instant situation is entirely different from the circumstances at issue in In re Gardner, Roe and Willey. For example, rather than a claiming a completely new chemical compound, the rejected claims are directed to methods of treating nervous tissue degeneration by transplanting differentiated neural cells into the subject in an amount effective to treat the nervous tissue degeneration. As pointed out in the Response of August 18, 2006, appropriate dosages and techniques for transplanting such differentiated neural cells are readily available to one of ordinary skill in the art. For example, Pluchino et al. (Pluchino et al. 2005, Neural stem cells and their use as therapeutic tool in neurological disorders, Brain Res Brain Res Rev., 48(2):211-9) at page 213, column 2, first paragraph, Pluchino et al. states that "When SDIA-induced dopaminergic neurons were transplanted into the 6-hydroxydopamine (6-OHDA)-lesioned mouse striatum, they integrated into the host tissue and remained positive for tyrosine hydroxylase (TH) expression." In addition, dosages and techniques for effective transplantation of differentiated neural cells, including situations where that transplantation resulted in treatment of nervous tissue degeneration such as occurs in Parkinson's Disease, were well known a decade prior to the filing date of the instant application. (See Nikkhah et al., J. Neuro., 14(6):3449-3461 (1994) "The results demonstrate a novel pattern of behavioral recovery induced by intranigral VM [differentiated neural cell] transplants in the rat Parkinson model"). Such information regarding dosages and techniques is not limited to in vitro, or even animal studies as human studies using transplants of differentiated neural cells have also been documented extensively.

(See, e.g., Defer et al., Brain, 119, 41-50 (1996) "The number of patients with Parkinson's disease receiving foetal neural transplants is increasing rapidly, and most investigators have shown a clinical benefit demonstrated by motor improvement in timed tests and self-reporting.") Accordingly, Applicants submit the Examiner's reliance the holding in In re Gardner, Roe and Willey is misplaced.

Applicants also note that the quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. In particular, the Federal Circuit has clearly stated that "'the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). In the instant situation, as noted above, there is a wealth of knowledge regarding the use of differentiated neural cells, which can be used to guide the necessary experimentation determine the optimal dosages and transplant techniques for any one particular therapeutic indication. However, such optimization would be merely routine experimentation in the art.

In light of the foregoing, Applicants submit that the pending claims encompass a method of inducing the neuronal differentiation of neural progenitor cells that is enabled by the disclosed specification, as well as a useful application of the invention that can be readily practiced by one of ordinary skill in the art. As such, Applicants assert that the presently amended claims are fully enabled by the specification, and therefore request that the rejection be removed.

The Examiner has rejected claims 1-5, 7-8, 14 and 16-17 under 35 U.S.C. § 112, first paragraph, as being unenabled. The Examiner contends that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or which it is most nearly connected, to make and/or use the invention. The Examiner contends that the specification is enabling for an *in vitro* method of promoting differentiation of neural stem cells comprising inhibiting ATF5, but does not, according to the Examiner, reasonably provide enablement for an *in vivo* or *ex vivo* method of promoting differentiation of neural stem cells comprising inhibition of ATF5 or transplanting the neural cells into a subject including humans and embryos. As described previously, the Examiner contends that the claims are unenabled due to the scope of the invention, the state and unpredictability of the art, and the alleged lack of working examples and adequate guidance in the specification.

Applicants believe that the pending claims are enabling for one of ordinary skill in the art. As stated previously, Applicants assert that the claimed invention has been reduced to practice through the working examples of the specification. In particular, at page 63, lines 1-30, Applicants demonstrate that the *in vitro* inhibition of ATF5 in neural progenitor cells with dominant negative ATF5 (NTAzip-ATF5), or siRNA directed toward ATF5, accelerates neurogenesis in the neuronal progenitors by specifically interfering with the function of endogenous ATF5. Applicants assert that the inhibition of ATF5 *in vivo* is a natural progression of the demonstrated success of ATF5 inhibition *in vitro*. Applicants have shown that the methods described in the specification and encompassed by the amended claims for *in vitro* inhibition of ATF5 are successful, and therefore establish the likelihood that *in vivo* ATF5

inhibition would also be successful. The Examiner contends that the therapeutic success of *in vivo* ATF5 inhibition, or *ex vivo* ATF5 inhibition followed by transplantation of the differentiated cells into a subject, has numerous obstacles that need to be overcome. As outlined above, Applicants, have provided a wide range of examples, both in animals and humans, establishing that differentiated neural cells of the invention can be used therapeutically. Furthermore, the art is replete with examples that will guide one of skill in the art in the general use of inhibitors such as ATF5 antibodies, dominant negative ATF5, or siRNA directed to ATF5. For example, Zecca et al., Blood, 97, 3995-3997 (2001) describe the therapeutic administration of antibodies, and Carroll et al., Mol. Cancer Thera., 1, 49-60 (2001) describe an andenovirus-mediated method that would be sufficient to introduce dominant negative ATF5 protein as well as to drive the expression of siRNA directed to ATF5. Applicants reiterate that clinically-optimized therapy is not the standard that is to be applied in determining whether the instant invention is enabled, rather it is whether one of skill in the art would be able to practice the invention without undue experimentation. Applicants respectfully submit that the instant application provides one of ordinary skill in the art sufficient guidance to practice the invention as encompassed by the presently amended claims, and therefore request that the rejection be withdrawn.

The Claims are Novel

The Examiner has rejected claims 1-3, 5, 7, 12, 14, 16 and 18 under 35 U.S.C. § 102(b) as being anticipated by Angelastro et al. In particular, the Examiner argues that the instant specification defines "a specific ATF5 inhibitor" so broadly that the non-specific inhibitor

of ATF5 disclosed in Angelastro et al., NGF, is encompassed by that definition, and thus anticipates the claims. Applicants respectfully traverse this rejection.

The relevant definition in the specification appears in paragraph [0145], which states:

> Accordingly, the present invention further provides a kit for use as an assay of a neural tumor, comprising an ATF5-specific agent and reagents suitable for detecting ATF5. **The ATF5-specific agent may be any agent reactive with ATF5 protein or nucleic acid**, including a nucleic acid probe which hybridizes to nucleic acid encoding ATF5, an antibody, and any of the agents described above.

Although the Examiner argues that the instant application teaches that ATF5 may be inhibited directly or indirectly, any agent capable of indirect inhibition would clearly fall outside the definition of ATF5-specific agents as such indirect inhibitors would not be reactive with ATF5 protein or nucleic acid. Accordingly, although NGF may be a non-specific inhibitor of ATF5, because the Examiner has not pointed to any evidence that it, itself, is reactive with AFT5 protein or nucleic acid, it cannot be construed as an ATF5-specific inhibitor. In light of the foregoing, Applicants respectfully request withdrawal of the instant rejection.

Claims 12-13 and 18 stand rejected under 35 U.S.C. § 102(e) as anticipated by either Jessell et al., (U.S. Patent Application Publication No. 2004/014210), or Yoshikazu et al., (U.S. Patent Application Publication No. 2003/0203489). In particular, the Examiner argues that the isolated differentiated neural cells of Claims 12-13 and 18 are indistinguishable from those cells described in the cited art, regardless of the process that was employed in generating them. Without acquiescing in the propriety of the instant rejection, and solely in the interest of expediting prosecution of the instant application, Applicants have canceled Claims 12-13 and 18,

rendering the instant rejection moot. Accordingly, Applicants respectfully request withdrawal of the instant rejection.

CONCLUSION

Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. Applicants believe that the invention described and defined by Claim 1-11, 14-17, 19, and 32 are in condition for allowance. Withdrawal of all rejections and reconsideration of the amended claims is requested. An early allowance is earnestly sought.

Respectfully submitted,

Steven P. Lendaris
Patent Office Reg. No. 53,202

Attorney for Applicants
BAKER BOTTS L.L.P.
30 Rockefeller Plaza
New York, NY 10112--4498
(212) 408-2500